DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
National Center for HIV, STD and TB Prevention
Division of Tuberculosis Elimination

Advisory Council for the Elimination of Tuberculosis
November 16-17, 2005
Atlanta, Georgia

Record of the Proceedings

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List of Participants

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Dr. Jennifer Flood
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Mr. Shannon Jones III
Ms. Sara Loaiza
Ms. Eileen Napolitano

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Dr. Amy Bloom (USAID)
Dr. Henry Blumberg (IDSA)
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Ms. Margie Scott-Cseh
Mr. Phillip Talboy
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Dr. Andrew Vernon
Dr. Wanda Walton
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Dr. Sundari Mase (Francis J. Curry National Tuberculosis Center)
Dr. Richard Menzies (McGill University)
Dr. Zohar Mor (Emory University)
Ms. Carol Pozsik (National Tuberculosis Controllers Association)
Mr. John Seggerson (National Coalition for the Elimination of Tuberculosis)

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ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS
November 16-17, 2005
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Minutes of the Meeting

The Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) convened a meeting of the Advisory Council for the Elimination of Tuberculosis (ACET). The proceedings were held on November 16-17, 2005 at CDC's Corporate Square Facility, Building 8, in Atlanta, Georgia.

Opening Session

Dr. Masae Kawamura, the ACET Chair, called the meeting to order at 8:30 a.m. on November 16, 2005. She welcomed the attendees to the proceedings and opened the floor for introductions. The list of participants is appended to the minutes as Attachment 1.

Dr. Ronald Valdiserri, the ACET Executive Secretary, announced that ACET meetings are open to the public and all comments made during the proceedings are a matter of public record. Members should be mindful of potential conflicts of interest identified by the CDC Committee Management Office and recuse themselves from voting or participating in these discussions.

Dr. Valdiserri presented plaques to formally recognize the diligent efforts of three ACET members whose terms have expired: Dr. Jeffrey Douglas, Ms. Teresa Garrett *in absentia*, and Ms. Eileen Napolitano. The participants applauded the valuable contributions the outgoing members have made to eliminate tuberculosis.

Update by the Acting Director for the National Center for HIV, STD and TB Prevention (NCHSTP)

Dr. Valdiserri was recently appointed to serve in the position of acting Director and covered the following areas in his report. Dr. Debbie Birx, the new Global AIDS Program Director recently began serving in this position and Darien Ogburn, the new Deputy Director for the Division of STD Prevention was recently selected. CDC announced its intention to expand the Coordinating Center for Infectious Diseases (CCID) from three to four centers and remove the Division of Tuberculosis Elimination (DTBE) from NCHSTP. CCID decided to maintain DTBE and all other existing programs in NCHSTP due to strong opposition to the proposal expressed by ACET and the National Tuberculosis Controllers Association (NTCA). The Division the Viral Hepatitis (DVH) will be added as a new division in NCHSTP. The next phase of CCID's reorganization is underway.

CDC initiated a new goals management process and identified 21 health impact goals in this effort. CCID was assigned primary responsibility for five of the 21 goals focusing on children 4-11 years of age to "grow safe and strong;" "healthy healthcare settings;" healthy institutions;" the "emerging infections scenario;" and the "influenza pandemic scenario." CDC's budget will be driven by priorities established by the goals management process.

NCHSTP's budget level is now flat because the federal government is still operating under a continuing resolution. For TB elimination activities, the Senate bill proposes an additional $637,000 above the FY'05 amount of $138.8 million and the House bill proposes level funding. House and Senate Committee language strongly encouraged CDC to continue and expand the TB vaccine cooperative agreement if possible and implement strategies to accelerate TB control and elimination activities among African Americans and U.S.-Mexico Border populations. The Senate Committee language also urged CDC to make resources available to states facing TB outbreaks among refugees.

NCHSTP deployed ~100 staff to support the national response to Hurricane Katrina. DTBE headquarters and field staff made outstanding efforts to locate and continue treatment for all 132 patients in Louisiana with active TB who were evacuated to other parts of the country following the hurricane. CDC, the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) published joint recommendations on TB control in the United States in the November 4, 2005 edition of the *Morbidity and Mortality Weekly Report* (*MMWR*). The document was distributed to ACET for review and wider distribution.

CDC's draft 2006-2015 Health Protection Research Guide (HPRG) will be published in the *Federal Register* on November 18, 2005 for a 60-day public comment period. The document will serve as a blueprint for all CDC research priorities. The public can submit comments to CDC on the HPRG by e-mail, regular mail or directly on the web site. An e-mail notice was circulated to ACET on November 15, 2005 about the upcoming *Federal Register* notice. NCHSTP is now asking ACET to decide whether a formal ACET statement or comments from individual members should be submitted on the HPRG.

Update by DTBE

Dr. Michael Iademarco, the DTBE Associate Director for Science, covered the following areas in his report. CDC completed eight Epi-AIDS in 2005 to investigate TB outbreaks in various locations, populations and settings. DTBE allocates funding of ~$800,000 to provide supplemental awards to programs that use Epi-AIDS as a follow-up to TB outbreaks. CDC temporarily assigns public health advisors to assist programs in implementing Epi-AIDS recommendations.

CDC estimates that as of October 7, 2005, 14,504 Hmong refugees had resettled in the United States; 238 refugees with TB had completed treatment; 910 persons remained in Thailand; 112 patients are still on treatment; and 26 patients were diagnosed with multi-drug resistant TB (MDR-TB). DTBE assisted in tracking 40 cases of TB in Hmong refugees in the United States. Of those, seven were MDR-TB cases. Efforts are underway to establish a database to track outcomes, relate these findings to overseas screening data, and assess the future impact of TB in Hmong refugees.

All states are now submitting isolates to CDC for genotyping. DTBE is collaborating with partners to identify strategies to utilize these data in the most effective manner, such as an outbreak or aberration detection system. DTBE recently completed its annual TB program manager's course with ~40 participants. Several new items will be added to the course in the near future, including a laboratory session; a cohort review process with a videotape and facilitator's guide; a revised and expanded document on forging partnerships for TB elimination; and patient education materials in three different languages.

Preliminary evaluation results were produced from the U.S.-Mexico Binational TB Referral and Case Management Project. The activity has retained strong policy support and will be expanded to new sites. Use of the system by U.S. Immigration and Customs Enforcement (ICE) detection centers has resulted in better coordination and

continuity of care. The evaluation of the pilot project led to several improvements. Most notably, 32% of card patients categorized as "moved" or "lost" in the national TB Information Management System (TIMS) had outcomes that could be determined by the project. Despite these achievements, insufficient funding for the CureTB information system and other components of the project is a considerable constraint.

The ATS/IDSA/CDC recommendations for TB control in the United States were published in a journal and the *MMWR* in November 2005. CDC convened a consultation in July 2005 with experts and investigators to discuss technical issues and review published and unpublished data to support the development of the QuantiFERON (QFT) Gold guidelines. CDC cleared and approved the draft guidelines for publication in the *MMWR* in December 2005. Two other sets of guidelines for TB infection control and contact investigations will also be published in the *MMWR* in December 2005. A document on TB in correctional settings is currently undergoing the CDC clearance process.

The 8th Semi-Annual TB Epidemiologic Studies Consortium (TBESC) meeting will be held on December 7-8, 2005 in Denver Colorado. The purpose of this event will be to review the TB research agenda and priorities; present recent findings from ongoing TBESC studies; and focus on research related to the development of tools for the diagnosis of latent TB infection (LTBI).

The Tuberculosis Trials Consortium (TBTC) recently held its semi-annual meeting to focus on key projects. TBTC Study 26 is comparing 12 doses of isoniazid (INH) and rifapentine versus a nine-month regimen of daily INH among persons with LTBI. To date, >5,000 of the 8,000 subjects needed for the study have been enrolled. Enrollment is expected to be completed in 2007 and the two-year follow-up period to detect TB will be completed in 2009. The event rate of TB was lower than expected and resulted in statistical and trial design issues, but the TBTC sites expect to adequately address these concerns and revise the study design to ensure a successful trial. DTBE intends to develop guidelines in 2010 to reflect the Study 26 findings.

TBTC Study 27 is a Phase II trial comparing two months of chest x-ray culture conversion after intensive-phase regimens of INH and rifampin/pyrazinamide (RZ) with either ethambutol (EMB) or moxifloxacin. The randomized trial is stratified by cavitation on chest radiograph and two sites in Africa versus 20 sites in North America. The study showed that culture conversion was equal in the two treatment arms, but a significant and unexpected difference was seen between the African and North American sites. As of March 2005, 336 patients were enrolled in Study 27.

Ongoing efforts are being made to develop new TB drugs that will shorten current regimens and improve the effectiveness of TB disease treatment. However, DTBE's budget constraints have negatively impacted TBESC and TBTC research projects because level funding appropriated by Congress does not account for rising costs from inflation each year. Most notably, some sites were released from TBESC or TBTC contracts.

DTBE responded to Hurricane Katrina by deploying >38 staff, establishing a TB help desk, and designing a communication and response strategy for persons in evacuation centers with suspected or confirmed TB. The objectives of these efforts were to facilitate sharing of patient information with NTCA and local TB controllers; provide education and guidance on identifying TB cases among evacuees; and respond to requests for information. All persons on TB treatment who were evacuated from Alabama, Louisiana and Mississippi following the hurricane were located to ensure continuation of therapy. New suspect cases among evacuees were identified. No patients were lost to treatment in Texas due to Hurricane Rita.

DTBE used a variety of methods to locate patients, including coordination and collaboration with local TB programs throughout the country, an extensive review of national registries to cross-match patient names, and searches on public web sites. DTBE also identified characteristics of TB patients from Louisiana who were unaccounted for to target efforts to persons at most risk for being or becoming infected. DTBE learned several lessons from its response to Hurricane Katrina. Timely sharing of information is critically important during a disaster. Activities by local TB programs in the field are the best methods to locate patients. Pre-event preparation may improve the timeliness of the cross-matching approach and address other potential problems.

ACET commended DTBE for its outstanding response to Hurricane Katrina and high level of communication with TB controllers throughout the country during the disaster. DTBE's response efforts have provided local TB programs with long-term benefits, such as stronger preparedness plans for a future disaster and guidelines for TB screening in makeshift shelters.

Reevaluation of Biological Agents of Public Health Importance for Bioterrorism

Mr. Joe Posid, of the CDC National Center for Infectious Diseases (NCID), provided an update on the reevaluation of biological agents of public health importance for bioterrorism. The first critical agents list was prepared in 1999 based on existing lists of

agents developed by a variety of sources. The 1999 list classified agents in one of three categories. "Category A" agents were defined as those with the greatest potential for adverse public health impact during a mass casualty. Most Category A agents require broad-based public health preparedness efforts, including improved surveillance, laboratory diagnosis and stockpiling of specific medications.

"Category B" agents were defined as those with some potential for large-scale dissemination with resultant illness. Category B agents generally cause less illness, result in fewer deaths and have a lower medical and public health impact than Category A agents. "Category C" agents were defined as those that serve as a current, potential or emerging threat to public health. Category C agents are not believed to present a high bioterrorism risk to public health, but could emerge as future threats.

Several actions were taken after the 1999 critical agents list was developed to account for more recent data. A public health assessment of potential biological terrorism agents was published in *Emerging Infectious Diseases* in February 2002. CDC and the National Institutes of Health (NIH) convened a critical agents meeting in 2004 with several goals. Processes for evaluating and prioritizing the critical agents were reviewed and discussed with 25 subject matter experts (SMEs).

Potential revisions or additions to the critical agents list were explored to improve the effectiveness of this tool in assisting the public health prioritization of bioterrorism threats. A determination was made on whether monkeypox, severe acute respiratory syndrome (SARS) and other agents that were not previously considered required evaluation for possible inclusion on the revised list. Next steps to complete the evaluation process and identify updated public health priorities for bioterrorism preparedness efforts were recommended.

The SMEs advised CDC and NIH to modify the rating system in several areas. For example, a determination should be made on whether pathogens should be sorted or continue to be grouped. "Public concern" should be deleted as a criterion for placing an agent on the list. SMEs should review and provide comments on agents in their respective areas of expertise rather than the entire list of 63 agents.

Another major change that occurred after the 1999 critical agents list was the development of Homeland Security Presidential Directives (HSPDs). HSPD-10 directs the Department of Homeland Security (DHS) to periodically assess bioterrorism agents to facilitate the allocation and prioritization of resources for preparedness planning and research and development. DHS is scheduled to release a draft report to the White House in January 2006 that will contain a prioritized list of biological threat agents

based on the risk, related consequences, data gaps and mitigation measures of each agent. DHS has asked CDC and other HHS agencies to continue to lead the development of a list of biological agents of public health importance for bioterrorism.

CDC is now taking several actions in response to this request. Data are being collected to support a pilot assessment of the public health implications of Category A, B and C agents based on infectious dose, infection-to-disease ratio, morbidity, mortality and long-term sequella. The list of 63 agents that will be produced will serve as a relative rather than an absolute ranking of threats based on the public health implications and availability of the agent. Guidance will be solicited from internal and external SMEs to create a ranking scheme for the agents. Because the entire U.S. government will use CDC's list of agents, intelligence, defense and public health agencies will fully participate in the development process. DHS plans to review CDC's list of agents every two to three years. CDC expects to produce its draft list of agents in January 2006.

Dr. Kawamura explained that this item was placed on the agenda in response to ACET's consensus recommendation during the previous meeting for MDR-TB to be reclassified as a Category B bioterrorism agent. ACET made several suggestions for CDC to consider in its ongoing efforts to reevaluate the list of biological agents of public health importance for bioterrorism.

- Include "route of transmission" as an additional factor. Collect and review solid data to support the critical need to distinguish between contact and airborne transmission.
- Separate elements of primary and secondary exposures because this approach will be extremely important for control measures and delivery of educational messages.
- Reconsider the decision to delete "public concern" as a criterion in placing an agent on the list because the necessary infrastructure and resources are not currently available to address new agents and develop antimicrobials or vaccines.

Overview of CDC's TB Surveillance Systems

Dr. Valerie Robison of DTBE reported that TB surveillance data are transferred from states to the TIMS database and then uploaded in the mainframe database. The TIMS and mainframe databases were recently reconciled with 259,910 records. DTBE implements the same process each year to collect and report TB surveillance data. An annual report and slide set of TB surveillance data are disseminated in both hard-copy

and electronic formats. The TB case count is finalized and a provisional database is created to develop an *MMWR* article for World TB Day. Data are checked and the data set is closed. DTBE's surveillance process adheres to agreements with states for data completeness, timeliness, consistency, privacy and confidentiality.

The TIMS help desk was established to provide support to the surveillance team and assist states in transferring data to CDC and addressing other technical issues. DTBE will change its surveillance process over the next three years to advance from a modem- to an Internet-based system. TIMS will no longer be used and states will have the option of selecting one of three systems to report TB data to CDC: the National Electronic Disease Surveillance System, TB Program Area Module (TB-PAM), or systems that are compatible with the Public Health Information Network. The long-range plan is for states to use one of two systems to report data. Data will be collected in multiple locations at CDC and then merged for national analyses.

Key findings from TB surveillance data collected in 2004 are highlighted as follows. TB cases reported in the United States have declined by 5%-7% each year over the past 12 consecutive years, but the decrease is now smaller. A decline of 45%-50% in the total number of TB cases will be needed each year to reach the goal of one case per 1 million persons by 2010. This target will result in a national case count of 350 cases assuming that the U.S. population grows to 350 million persons in 2010. The number of TB cases reported in the United States decreased from 16,309 in 2000 to 14,517 in 2004. The TB case rate also declined from 5.8/100,000 in 2000 to 4.9/100,000 in 2004.

By race/ethnicity, minority groups accounted for 82% of all reported TB cases and whites accounted for 18%. The 29% burden in Hispanics accounted for the single largest percentage of TB cases among all racial/ethnic groups. By origin, the number of states with at least 50% of TB cases in foreign-born persons increased from seven states in 1994 to 22 in 2004. TB cases in all racial/ethnic foreign-born populations decreased over time except in black non-Hispanics. The 2004 annual report is now available on the CDC web site. Changes DTBE has made to improve the accuracy of data are documented. DTBE is now soliciting input from ACET on whether the annual report and tables of TB surveillance data are meeting the needs of users, partners and other customers.

New TB Surveillance Initiatives

Dr. Thomas Navin of DTBE described five major efforts DTBE is undertaking to improve the accuracy and accessibility of TB surveillance data. One, the Online TB Information

System (OTIS) was recently launched on the CDC web site as a national TB surveillance data set with cross-tabulations, figures and maps. The public can use OTIS to make ad hoc queries on 22 variables in the report of a verified case of TB (RVCT). However, OTIS data are suppressed or aggregated to maintain patient confidentiality.

Two, the National Surveillance System for Severe Adverse Events (SAEs) associated with LTBI treatment is used to evaluate and revise guidelines and assist healthcare providers in preventing SAEs. For purposes of the system, DTBE defines an "SAE" as hospitalization or death of a patient following LTBI treatment. DTBE requests reports of SAEs and then conducts onsite investigations to obtain more details and determine if the SAE was due to LTBI treatment. RZ reporting was implemented in 2001 and the system was expanded in 2004 to report SAEs from all LTBI treatments.

Of the 76 SAEs reported to the system to date, 50 were associated with RZ, 20 with INH and six with EMB/pyrazinamide (PZA). Only six SAEs were reported to the system after DTBE published its revised guidelines in August 2003 recommending against the use of RZ, but the completeness of reporting is questionable. To address this concern, DTBE will formally establish collaborations with the Food and Drug Administration (FDA) and other agencies and more widely publicize the SAE surveillance system. The system is currently limited to numerator data. Additional investments will be needed to include denominator data. DTBE is now requesting guidance from ACET on effective strategies to minimize fears of legal consequences among healthcare providers in reporting SAEs, such as an anonymous web site to submit information.

Three, all 50 states are now participating in the National Genotyping Program to detect TB outbreaks with universal genotyping. As of November 4, 2005, 7,760 of the 12,704 genotyped isolates were in clusters, but not all of these clusters represented outbreaks. This initiative is based on findings from the National TB Genotyping and Surveillance Network in which seven sites were funded from 1996-2000 to demonstrate the programmatic utility of genotyping.

In several large clusters that were recognized, only nine epidemiologic links were detected among 207 patients across six of the seven funded sites. Universal genotyping data can be used to detect TB outbreaks sooner, but several challenges must first be addressed. Feasible approaches are needed to share cluster results among jurisdictions. Computer-based aberration detection algorithms are being developed to effectively review, analyze and flag clustered isolates. RVCT and genotyping data need to be linked.

Four, the current revised draft of RVCT data was reviewed by TB controllers in 2003, considers additional variables for genotyping data and includes 12 new data elements. TB-PAM is expected to be launched in ~2 years with the new RVCT data. Input will be solicited from states in the current revision of the RVCT data.

Five, the data accuracy project was designed to measure and improve the accuracy of RVCT data. Previous studies have demonstrated that TB surveillance data are complete and disseminated in a timely manner. Overall, DTBE's goal is to assist states in using better surveillance data to improve decision-making. This goal will be achieved with improved surveillance data through the data accuracy project and RVCT revisions; better access to data through OTIS; and new systems to detect outbreaks and report SAEs.

ACET commended DTBE on its extensive efforts to obtain broad input from TB controllers and programs throughout the country on making TB surveillance data more accessible and usable. Several suggestions were made to DTBE to strengthen the TB surveillance systems.

- Include correctional facilities and homeless shelters as additional variables in the genotyping data set to pinpoint potential outbreaks in these settings.
- Incorporate additional variables in the RVCT data set to obtain information on TB patients in ICE custody and determine the custodial agency for TB patients in correctional facilities.
- Develop strategies at this time to resolve problems that may arise in the future with the TB surveillance systems related to Health Insurance Portability and Accountability Act requirements and Institutional Review Board approval.
- Disseminate guidance to clearly and explicitly state DTBE's definition of an "SAE" associated with LTBI treatment.
- Use geographical mapping to detect different TB strains in certain jurisdictions and leverage funds for local programs in areas with the highest TB burden.

Domestic Returns from TB Control Investments in Other Countries

Dr. Richard Menzies, of McGill University, reported that the overall global TB incidence is increasing, particularly in Eastern Europe and sub-Saharan Africa. TB in low- and middle-income countries affects high-income countries because the disease is easily carried and LTBI is difficult to detect or prevent. In 1990, 120 million persons

permanently lived in countries other than where they were born compared to 150 million persons in 2000. Parallel trends of an increasing proportion of TB in foreign-born persons are seen in Canada and the United States because the TB incidence is declining in Canadian- and U.S.-born persons. These trends emphasize the importance of stable TB incidence and increased case rates in foreign-born persons.

Administrative, technologic and biologic limitations are associated with TB screening and prevention efforts among immigrants at the time of entry to a country; detection of migrants with active TB or LTBI; and treatment at the source to enhance TB control in migrant source countries. Most notably, LTBI tests are flawed and treatment is lengthy, costly, unpleasant and may be associated with severe side effects. Migrants who return to their countries of origin may become infected or reinfected with TB. A chest x-ray is the most widely used TB screening method internationally, but sensitivity may be poor and technical problems may arise overseas in interpreting and reproducing results. Tuberculin skin tests (TSTs) have minimal sensitivity with advanced TB disease and poor specificity due to BCG and other factors. TSTs also produce false-positive and false-negative results.

Current estimates show that nearly 2 million "deportable located" individuals reside in Canada and the United States each year. Not all of these migrants are screened, such as visitors who reside in Canada and the United States <6 months. Most students from other countries who enter Canada and the United States are tested, but TB screening policies are highly variable in source countries. TB screening and infrastructure are also insufficient for the large number of temporary workers who migrate from other countries to Canada and the United States. Efforts to improve and sustain TB control in low-income countries are extremely difficult due to inadequate infrastructure, poorly trained staff, inferior or no drugs, HIV co-morbidity, increased drug resistance, medical errors, patient non-compliance to therapy, and increased TB rates that overwhelm existing services.

Dr. Menzies and colleagues wrote a paper that was published in the *New England Journal of Medicine* in September 2005 on the impact of U.S. investments in TB control in other countries. The cohort was a diverse group of young persons who migrated from the Dominican Republic, Haiti and Mexico to the United States over a 20-year period. The study compared three strategies. The "status quo" was current TB control programs with existing case detection, completion of treatment in the three countries, and current chest x-ray screening of migrants to the United States. An "expansion of directly observed treatment short-course" (DOTS) was nationwide DOTS coverage with program indicators that met targets established by the World Health Organization

(WHO). "TST screening" was tuberculin screening added to current screening for all legal immigrants at U.S. entry.

The objectives of the study were to predict the impact of DOTS expansion or TST screening on TB incidence, mortality and TB-related costs from both health system and societal perspectives after the migrants arrived in the United States. The cohort was assumed to have a prevalence of active TB and LTBI based on the annual incidence and risk of infection in the respective source country and age of the individual subject. The literature was extensively reviewed and analyzed to design models for the study and determine the probability of each event, such as developing TB disease or LTBI, being diagnosed and cured, and surviving.

The study assumed that the United States would pay for DOTS expansion in the three countries to provide additional training, infrastructure and supervision of healthcare personnel. This investment would not support salaries to provide direct care to TB patients. Expenses to patients and their families as well as costs for TB care, screening and lost productivity were examined. However, migrants who entered the United States without TB and developed the disease after arrival served as the major cost. The study showed that a 6% decline in incidence would reduce the risk of TB infection and LTBI prevalence. Of TST-positive persons, 21% were projected to complete the nine-month INH regimen.

DOTS expansion was found to play a significant role in TB mortality in the source countries in which a $3 million investment would cover 50% of a country. However, DOTS expansion only made a small difference in legal immigrants with continued chest x-ray screening, the same TB control programs and stable incidence in the countries of origin. DOTS expansion had a larger impact on illegal immigrants and visitors.

Net savings to the United States from investments in DOTS expansion over a 20-year period were projected to be $108 million with a $34 million investment in Mexico; $6 million with a $6 million investment in the Dominican Republic; and $10 million with a $3-$4 million investment in Haiti. The total cost for DOTS was projected to be $2.6 billion over 20 years for TB control in Mexican immigrants in the United States. A return on the U.S. investment in Haiti would be seen earlier in the 20-year time period than the Dominican Republic or Mexico due to the higher TB rate and smaller population in Haiti. In all three countries, the total societal savings of $128 million over 20 years were primarily from illegal immigrants and visitors.

The sensitivity analysis showed that DOTS expansion would generate the same cost savings to the United States even if the initial costs doubled, annual costs for drugs and

staff supervision were added, the impact from DOTS was less, or return visits of migrants to the United States were frequent or longer. The same analysis demonstrated that DOTS expansion would produce greater savings if more migrants entered the United States, HIV seroprevalence increased or drug resistance was higher.

TB patients and their families collectively would spend $78 million in the United States, but DOTS expansion in the countries of origin would result in savings of $31 million. DOTS expansion would also result in cost savings for each life saved in the Dominican Republic, Haiti and Mexico. TST screening had a larger impact than DOTS expansion on societal costs over a 20-year period in which 716 TB cases would be averted among legal immigrants and the net increased cost would be ~$370 million or ~$500,000 per case averted.

The authors reached several conclusions based on the study findings. A U.S. investment in DOTS in source countries with a higher TB incidence will result in cost savings to the United States. Returns on these investments will be much more dramatic in the source countries than the United States. U.S. investments will have only a modest impact on the numbers of TB cases, but the savings directly reflect significantly lower costs to treat cases in the Dominican Republic, Haiti or Mexico than the United States. The United States will see returns from its investments in DOTS expansion in 10-15 years depending on the infrastructure of the individual country.

The magnitude of cost savings is sensitive to key assumptions, such as the rate of decline in TB incidence. Targeting TB control efforts to countries with the most migrants will generate the largest returns on investments. U.S. savings are in addition to large savings in the countries of origins of migrants. Improved TB control efforts in source countries will produce economic benefits for all countries. Overall, the study makes a strong case for countries to cooperate and collaborate in making targeted overseas investments in TB control.

Dr. Kawamura pointed out that the U.S. investment in other countries for TB control is a provocative approach and will produce both economic and humanitarian benefits for all countries. She confirmed that this issue would be revisited on the following day for ACET to identify appropriate action steps to take with the study results.

Sputum Specimens to Diagnose Pulmonary TB

Dr. Henry Blumberg is the ACET liaison to IDSA. He described activities that are being conducted by Grady Memorial Hospital in Atlanta, Georgia to determine the number of

sputum specimens needed to diagnose pulmonary TB. Communities surrounding Grady have incredibly high TB rates that are similar to some developing countries. If Grady was a state, the number of its TB cases reported would be ranked as the 28th highest in the country and would surpass the states of Connecticut and Oregon. The number of TB patients who received care at Grady decreased from 1997-2004, but the decline has been level over the last few years.

Grady established and strictly enforces rigorous criteria for its TB isolation policy. Patients with a physician's order for a sputum acid-fast bacillus (AFB) smear and those admitted with rule-out TB, a differential diagnosis of TB, or HIV infection with an abnormal chest x-ray must be placed in an airborne infection isolation room (AIIR). Patients can be removed from an AIIR based on negative results from three sputum AFB smears. Of Grady's 1,543 patients placed in AIIRs per year, 5.4% are adult admissions and 12.8% are medical and surgical admissions. Overall, only 10% of patients placed in AIIRs actually have TB.

Grady implemented several strategies to improve its efficiency in caring for patients with suspected TB and those who are placed in AIIRs in accordance with the TB isolation policy. A dedicated 26-bed respiratory isolation unit was established and decreased the average time from 5.6 to 3 days to obtain three negative sputum AFB smears, rule out TB and remove patients from isolation. The isolation unit resulted in a savings of >3,000 respiratory isolation days per year. Broad efforts to capture any individual who may have active TB have been fairly successful in which 95% of patients subsequently diagnosed with pulmonary TB are isolated. The overall rule-out ratio of the number of patients placed in isolation who actually have TB is 10:1 with a range of 21:1 for HIV-positive patients and 3:1 for HIV-negative patients.

CDC previously recommended sputums for AFB smears and cultures 24 hours apart, but the draft 2005 TB infection control guidelines now recommend three sputums at least eight hours apart and at least one in the early morning. Grady conducted a study at its facilities from 1997-2000 after CDC published the previous TB infection control guidelines. The Grady Clinical Microbiology Laboratory processed AFB smears and cultures of respiratory specimens using a standard methodology, concentrated method fluorochrome staining of AFB smears, and broth-based and solid media for cultures.

Of 425 patients with culture-confirmed pulmonary TB, 67% were smear positive with specimen 1, 71% with specimen 2 and 72% with specimen 3. AFB smear sensitivity for both HIV-negative and HIV-positive patients only increased by 1% when the third specimen was collected. Over the four-year study period, only one person would have

been missed each year if two rather than three AFB smear specimens had been collected.

A multi-variate analysis of factors associated with AFB-positive smears showed that HIV-negative patients are more likely to be smear-positive than HIV-infected patients. Upper and middle lobe infiltrates and cavitary lesions were also associated with AFB-positive smears. In another analysis of the study, the entire sample size of 415 patients had at least one culture that was positive for *Mycobacterium tuberculosis*. The culture positivity rates were 93% with specimen 1, 98% with specimen 2 and 100% were specimen 3. This analysis also showed that most patients were diagnosed with two specimens.

Grady reached several conclusions based on the study results. Two respiratory specimens for AFB smear and culture were generally adequate in diagnosing pulmonary TB. The addition of a third specimen produced limited benefits. Three AFB specimens must be collected to rule out pulmonary TB, but significant cost savings and increased efficiency in using AIIRs would be achieved if the requirement was changed to two AFB specimens. Grady plans to implement this change early in 2006.

ACET emphasized that a policy change to collect two rather than three AFB specimens to rule out pulmonary TB must be based on solid data to support the local TB epidemiology. This approach cannot be taken at the national level due to the diversity of TB burdens and other factors in jurisdictions. ACET advised Grady to use data from the study to develop economic models and perform sensitivity analyses.

Improving the Diagnosis of TB

Dr. Sundari Mase, of the Francis J. Curry National Tuberculosis Center, presented key results from a systematic review that was conducted. The research was designed to answer two key questions. First, what is the yield from serial sputum smear examinations in evaluating smear-positive pulmonary TB? Second, is the yield from three AFB sputum smears substantially higher than two smears? Findings from these research questions can be used to address critically important issues. In high-burden resource-poor countries, case detection can be improved by optimizing smear microscopy techniques. The cost and burden of performing large numbers of smears can be reduced. In low-burden developed countries, hospitalization costs associated with evaluating pulmonary TB suspects can be decreased.

A previous literature review of the yield from serial smears with or without serial cultures showed that two smears were successfully utilized in countries with limited resources. The analysis further concluded that three smears were no less convenient, but appeared to be better in locating the vast majority of patients. Criteria for the current systematic review included original studies, published articles, manuscripts accepted for publication, letters, dissertations and abstracts that evaluated TB suspects with ≥3 AFB sputum smears and reported data to calculate the incremental yield (IY) from specimens 2 and 3. Data that did not answer the two research questions as well as animal studies, case studies and reports, review articles, commentaries and non-English language publications were excluded from the systematic review.

A variety of databases were used to search the literature. Of the 3,538 potentially relevant citations identified, 36 articles from 42 studies were included in the systematic review. For purposes of the study, "reference standard" was defined as a mycobacterial culture; a "smear-positive case" was defined as a positive result in at least one of three smears; and a "main outcome measure" was defined as an IY from AFB sputum smear 3. The cumulative yield (CY) from serial smears was also calculated. For studies that used a reference standard, the IY and CY from sensitivity were calculated with all culture-positive or all smear-positive patients as the denominator. For studies that did not use a reference standard, the IY and CY from smear positivity were calculated with all smear-positive patients as the denominator.

Sample calculations were conducted to determine the IY and CY from smear positivity and sensitivity with denominators of 100 smear-positive or culture-positive patients. The IY and CY were also calculated in various subgroups based on use of the reference standard, number of smears collected, study design, stain used and smear preparation. Other subgroups were formed based on prospective versus retrospective studies, conventional versus fluorescent microscopy, and direct versus concentrated smears. The mean of patients in the study was 1,033 using smear positive as the denominator and 144 using culture positive as the denominator.

Of the 42 studies included in the systematic review, 52% used a reference standard and 43% did not; 12% collected four AFB sputum smears and 5% collected eight; 43% were prospective and 52% were retrospective; 93% enrolled consecutive patients and 7% did not report this variable; and 57% used conventional microscopy, 38% used fluorescent microscopy; 38% used a concentration method and 43% used direct smear microscopy.

Key findings from studies that used or did not use a reference standard are as follows. Of the 19 studies using smear-positive patients as the denominator, the IY was 84% from smear 1, 13% from smear 2 and 3.6% from smear 3. Of the 11 studies using

culture-positive patients as the denominator, the IY was 57% from smear 1, 9% from smear 2 and 3.8% from smear 3. These results were similar for prospective and retrospective studies that used smear positivity, direct smears, a concentration method or conventional microscopy as the denominator. However, the IY from smear 3 was lower when fluorescent microscopy or culture positive was used as the denominator.

The mean IY from smear 3 ranged from 1%-5% when the subgroup was analyzed. The IY from smear 3 was found to be <5% regardless of the method used to analyze the data. The IY from smear 3 will be even lower if IYs from smears 1 and 2 are further improved by microscopy methods. Removal of AFB sputum smear 3 would have a much greater impact on case finding if the WHO case definition of "smear positivity" is retained. On the one hand, obtaining two smears per suspect will decrease the workload for technicians, improve the quality in reading two smears and result in reduced costs. On the other hand, the proportion of TB cases detected will decline and more infectious cases will occur due to LTBI.

A "real world" analysis on the impact of eliminating AFB sputum smear 3 was also conducted in the systematic review. A paper published in 1996 found that the result of each smear-positive case in Malawi was ten contacts, 840 additional infections and an additional 84 cases. A paper published by the University of North Carolina-Chapel Hill in 2000 concluded that modifying hospital policy to collect two rather than three smears per suspect would not change the risk for transmission because the IY from smear 3 was 0%. The study also showed a $32,000 cost savings in one year due to 270 fewer patient days in airborne precautions.

The strengths of the systematic review are a comprehensive literature review of relevant articles from 1959 to the present, limited publication bias, independent reviewers and analyses of subgroups to account for the large amount of heterogeneity in the studies. The weaknesses of the study are an inability to differentiate among specimens 1, 2 and 3, absence of a blind study design, no cost-effectiveness analysis, and a difference in WHO's case definition of "smear-positive pulmonary TB cases." Recommendations for future studies were formulated and next steps were identified based on findings of the systematic review. Explicit criteria should be developed for patient selection; a prospective and consecutive sampling protocol should be applied; and a reference standard should be used. Future studies should be designed with a blind protocol and structured to produce both culture and smear results.

The impact of two versus three AFB sputum smears should be extensively analyzed in HIV-infected patients because microscopy typically produces a low yield in this population. The policy implications of collecting two versus three AFB sputum smears

per TB suspect should be discussed. WHO's case definition of "smear-positive pulmonary TB cases" should be reviewed. WHO plans to disseminate a consensus statement advising countries to continue to collect three AFB sputum smears unless a laboratory evaluation of the IY from smears shows that the removal of smear 3 will not result in a huge decrease in TB case detection.

Future Opportunities and Challenges for TB Clinical Trials

Dr. William Burman is an ACET member. He described opportunities and challenges for TB clinical trials that will need to be addressed over the next ten years. Several factors emphasize the critical need to improve DOTS. No actions have been taken in TB drug development since 1968, but HIV, drug interactions and other complications have occurred since this time. In an unpublished study by the Denver Public Health Department, 30% of non-alcoholics had significant toxicity from TB therapy and 7% had hepatitis. Data published in 1999 showed that up to 20% of patients in a rural program in Hlabisa, South Africa did not complete 180 days of TB treatment.

The prevalence of MDR-TB among new TB cases represented $\geq$6% of previously untreated TB cases from 1994-2002. Rifampin (RIF) has more clinically significant interactions than any other drug in the pharmacopeia and is particularly problematic for HIV patients. Bothersome and serious side effects from RIF are frequently reported and would not be tolerated with drugs for diabetes and other chronic diseases. The six-month "short course" is relatively expensive and is still too lengthy for patients to complete treatment. The rising rate of drug resistance threatens the effectiveness of DOTS in some parts of the world.

Evaluation of five new TB drugs in human trials in 2005 represents an unprecedented opportunity to dramatically improve and revolutionize treatment of active TB and LTBI. Data from animal models show that TMC207 is better than INH, PZA and RIF. In combination with other drugs, TMC207 can produce complete sterilization of TB in animals in <2 months. Preliminary data from animal models show that nitro-imidazo-oxazoles can shorten a course of TB treatment by three to four months. PA-824 alone shows nearly the same efficacy as INH and RIF combined when the drug is given in the continuation phase of conventional therapy after the first two months.

The new drugs in development show extremely potent activity in animal models of TB therapy, allow treatment to be completed in two to four months, and are highly active when given one to two times per week. Combinations of new drugs may be even more potent. Most notably, a twice-weekly regimen of RIF/moxifloxacin may allow treatment

to be completed in three to four months. Feasible goals for TB clinical trials can be established for the next ten years based on the promise of these new drugs. Treatment duration for active TB and LTBI can be shortened to ≤2 months. Highly-efficacious intermittent therapy can be given once or twice per week. TB therapy can be better tolerated due to decreased side effects and fewer interactions with other drugs.

The potential exists to shorten TB therapy from six to two months. Several studies have demonstrated that the mouse model of TB treatment is predictive of results in humans so long as human pharmacokinetics are carefully replicated. Clinical trials will be guided by the mouse model to identify sterilizing activity and effects from multi-drug regimens, but large human studies will still be needed. The mouse model of TB treatment does not predict toxicity, requires a narrow range of inoculum, and does not appear to model pulmonary cavitation and other high-risk subgroups.

Surrogate markers can be applied in early clinical trials to address these issues. Early bactericidal activity (EBA) is a marker of quantitative cultures in sputum of patients in the first few days of therapy. Small sample sizes of 10-12 patients per arm are required to perform robust comparisons of this marker. EBA identifies doses to be evaluated in Phase II trials and compares members of the same drug class to select the most promising agent for evaluation in Phase III trials. However, EBA is limited to assessing single drugs rather than regimens. The traditional EBA of 0-2 days does not correlate with sterilizing activity.

Sputum culture conversion is a marker that showed the best correlation to relapse rates at two months in previous studies. Sample sizes of 150 patients per arm are required to evaluate this marker. The increased two-month culture conversion predicts the ability to shorten therapy while retaining low relapse rates. In addition to applying surrogate markers, problems with previous TB clinical trials that led to the six-month regimens must be thoroughly examined as well. The presence of high-risk subgroups was concealed by overall response rates. Decreased efficacy with intermittent administration during the first two months of therapy was not detected. Uncertainties with dosing, drug-induced hepatitis and other determinants of unusual and severe toxicity were not resolved.

Lessons learned from previous TB clinical trials should be reviewed to avoid duplicating these errors. Regimens rather than individual drugs should be evaluated to account for different points in therapy and various companion drugs. Many regimens may need to be assessed to identify the optimal combination of potency, tolerability and intermittence. EBA and two-month sputum culture conversion should be applied as

surrogate markers. Phase III trials should be designed with larger cohorts to detect clinically-relevant differences in failure, relapse and rates of serious toxicity.

TB regimens should be evaluated in HIV-infected persons, other key subgroups and diverse patient populations around the world. Methodologies should be developed to resolve problems in shortening TB therapy from six to two months. Phase II trials should be liberally used to evaluate the number of doses, combinations and dosing frequencies and identify the optimal new regimen for ultra-short course therapy. Large Phase III trials should only be used to evaluate the efficacy and toxicity of promising new regimens.

Global capacity for TB clinical trials does not currently exist because evaluations of new TB drugs are entirely focused on fluoroquinolones. TB clinical trials funded by CDC, NIH, European groups and other organizations are facing decreased resources, level capacity and limited study designs.

To enhance capacity and markedly accelerate clinical testing of new TB drugs and regimens, a modest annual investment of $10 million would be needed for eight new trial sites, enrollment of 1,500 patients per year, expansion of the data and operations center, and additional microbiology and pharmacokinetic laboratory activities. After the initial evaluation, an additional investment of $8 million per year would be needed to advance Phase III and IV testing of new regimens. Current annual funding for clinical trials is $14 million for TB and $500 million for HIV/AIDS. The proposed annual funding of $32 million for TB clinical trials would still be considerably less than HIV/AIDS.

Dr. Valdiserri indicated that the Treatment Action Group (TAG) sent a letter dated November 14, 2005 to Dr. Kawamura. A statement of individuals from communities affected by TB was attached to the letter and recommends that leaders, governments and all sectors of society take 12 specific action steps, such as “scaling up research on new tools to stop TB” and “discovering new TB vaccines.” Copies were shared with ACET.

ACET’s suggestions to accelerate clinical testing of new TB drugs and regimens are outlined below.

- Develop and distribute a formal statement by ACET to the HHS Secretary to emphasize several important points. For example, the additional investment of $10-$18 million per year for TB clinical trials is a critical need. The proposed funding is extremely modest compared to resources allocated to HIV/AIDS, avian influenza and anthrax, particularly in light of

the TB mortality rate of ~2 million deaths per year. Tremendous benefits will be gained at the global level from new resources, such as the shortened TB regimen from six to two months. The source of the additional investment in TB research should be from new dollars rather than a diversion of existing funds from TB programs.

- Make stronger efforts to leverage more HIV/AIDS funds by emphasizing that TB is the largest cause of death in HIV patients around the world.
- Document the impact of the global TB epidemic on the United States.
- Describe needs for TB research other than clinical trials, such as new diagnostics.
- Replicate effective and successful strategies that were used in HIV/AIDS to increase advocacy for and public interest in TB. For example, partner with ATS, TAG and other groups in aggressive efforts to increase funding for TB research. Establish new relationships with private-sector groups that are developing TB drugs.
- Explore opportunities to include TB research in CDC's HPRG.
- Urge CDC to partner with NIH in creating a collaborative body at the federal level to coordinate TB research activities.

A motion was properly placed on the floor and seconded by voting members for ACET to take the following actions. Drs. Burman and Kawamura will draft ACET's formal statement on the proposal to invest an additional $10-$18 million per year for TB clinical trials. Dr. Watkins-Bryant will initially review the statement to ensure that the language is consistent with priorities established by the HHS Secretary. Efforts will be made to obtain written support from the CDC, CCID and DTBE Directors before ACET's statement is sent to the HHS Secretary. The statement will be presented to ACET on the following day for review and formal approval. **The motion was unanimously approved.**

ACET Statement on TB Elimination and the Role of Primary Care

Dr. Kawamura announced that this item was placed on the agenda in response to an extensive discussion during the June 2005 meeting. ACET previously agreed that a statement should be written to reach out to primary care providers (PCPs) who diagnose TB and passively locate cases. Several members pointed out that diagnoses are often delayed because PCPs typically do not consider TB when patients present with symptoms.

The draft statement was distributed to ACET for review and comment. ACET's suggestions to refine the document are outlined below.

- Shorten the statement, but maintain the critically important background section because many PCPs have no knowledge, interest or understanding of TB.
- Tailor messages to reach specific target audiences of PCPs, such as rural practitioners and medical societies representing state and local providers.
- Include a short "frequently asked questions" (FAQs) section to address specific issues of concern to PCPs, such as appropriate steps to take in reporting suspect TB cases to public health agencies and reimbursement policies for treatment of uninsured TB patients.
- Provide references and locations of educational materials that have been developed by CDC and translated into different languages.
- Increase interest in TB among PCPs by including information on QFT-Gold, TB screening and more specific blood tests that may soon be available.
- Encourage DTBE to partner with the American Medical Association (AMA) in developing effective messages for PCPs and an appropriate format for the statement, such as a multi-fold pamphlet.
- Distribute the statement in venues other than World TB Day. For example, mail the statement to PCPs on CDC rather than ACET letterhead to increase the relevance, importance and priority of the document. Publish the statement in *JAMA* or another journal as the first in a series of TB case studies.

Dr. Kawamura noted that the comments did not indicate consensus on next steps ACET should take to strengthen the role of PCPs in TB elimination. She confirmed that this issue would be revisited on the following day. In preparation of the discussion, she asked ACET to consider whether the current version of the statement should be given to DTBE for revision and dissemination or if ACET should formally establish a new "Primary Care Provider Workgroup" to specifically address this issue.

Update by CCID

Ms. Kimberly Lane is the CCID Senior Advisor to the Chief Management Official. She covered the following areas in her status report. CCID is the largest of CDC's four coordinating centers with a workforce of 4,643 staff and a $4.099 billion budget that represents >50% of CDC's resources. CCID plans to announce permanent directors for

three of its centers in early December 2005. CCID's organizational structure is being redesigned to more clearly define its leadership role and strengthen support for the changing environment and global impact. These changes include CDC's increased visibility, an accelerated emergence of infectious diseases, rapid changes in technologies, inadequate funding, new coordinating centers, and different strategies for SARS, Hurricane Katrina, anthrax and other new public health responses.

CCID is also redesigning its organizational structure to improve internal factors. Roles, responsibilities and accountability of leaders and staff will be better clarified. Information exchange within and between organizational units will be improved. Business services and decision-making will be more efficient and streamlined. The public health impact will be maximized to ensure excellence of staff, science and programs. CCID extensively solicited input from stakeholders through workgroup sessions, focus groups, surveys, individual meetings and electronic mailboxes to redesign its organizational structure.

CCID's new center, institute and office (CIO) structure is outlined as follows. CIO 1 houses the National Immunization Program and components of NCID that support immunization activities. CIO 2 houses NCID components that focus on food-borne, water-borne and zoonotic diseases. CIO 3 houses NCHSTP and DVH to address common target populations and prevention strategies for HIV, STD, TB and hepatitis at both domestic and global levels. CIO 4 houses divisions and programs that focus on cross-cutting epidemiologic and laboratory activities. CCID will also be supported by a Strategic Business Unit and a Strategic Science and Program Unit for formal integration of administrative, scientific and technical functions across organizations.

CCID is now attempting to identify appropriate names for its "infectious disease" centers because each program has an existing brand and public recognition. Input will be extensively solicited from federal, state, local and private partners in this effort. CCID intends to achieve this goal by circulating a blast e-mail message to partners in the next week and convening a meeting in 2006 with ACET representatives and other partners to discuss strategies to effectively interact with CCID. Appointments of permanent staff will also assist in enhancing linkages between CCID and its partners. CCID expects to stand-up the new structure in October 2006 and complete refinement and implementation of the new organizational design by October 2007.

Dr. Valdiserri announced that the NCID Board of Scientific Counselors will hold a meeting on November 30-December 1, 2005 in Atlanta, Georgia. The chairs of ACET and other advisory committees to CCID centers have been invited to attend the meeting to discuss the establishment of a unified advisory board to CCID.

With no further discussion or business brought before ACET, Dr. Kawamura recessed the meeting at 5:00 p.m. on November 16, 2005.

Current ACET Business

Dr. Kawamura reconvened the meeting at 8:30 a.m. on November 17, 2005 and entertained a motion to accept the previous meeting minutes. The motion was properly moved and seconded by Drs. Fleenor and Fluck, respectively. The June 8-9, 2005 ACET Meeting Minutes were **unanimously approved** with no changes or further discussion.

The action items and agenda items raised over the course of the meeting are outlined below.

Action Items

- Mr. Posid will provide DTBE with the complete list of public health factors that will be considered in developing CDC's list of bioterrorism agents. DTBE will distribute the document to ACET.
- Mr. Posid will provide DTBE with CDC's response to ACET's July 2005 letter requesting that MDR-TB be reclassified as a Category B bioterrorism agent. DTBE will distribute the letter to ACET.
- DTBE will circulate the current revised draft of RVCT data to ACET for review and input.
- DTBE will collaborate with one of the Regional Training and Medical Consultation Centers to develop an effective format for ACET's statement to PCPs after the content is formally approved.
- Dr. Valdiserri will obtain information about CDC's representation on HHS workgroups that were recently established to develop a ten-year plan to share electronic medical records. He will report his findings to ACET.
- The Division of Global Migration and Quarantine (DGMQ) will provide DTBE with the draft technical instructions for overseas panel physicians. DTBE will distribute the document to ACET for review and comment.
- Drs. Burman and Flood will review CDC's HPRG; formulate preliminary recommendations on the three broad areas of new TB diagnostics, drug development and personal respiratory protection; and circulate their findings to ACET for review and comment.

Agenda Items

- Detailed update by DTBE and DGMQ on the TB outbreak in Hmong refugees, including the status of the assessment of case management quality.
- Update by DTBE on actions taken in response to recommendations by the ACET Foreign-Born Workgroup.
- Overview by the CCID Director on ACET's long-term relationship with CCID.
- Overview of binational case management of TB patients, including legal issues, authorities of various governmental entities and electronic data exchange.
- Update by the HHS Office of Minority Health on racial/ethnic disparities, including TB control strategies or best practices that are being implemented in urban settings, African American communities and other populations of color.
- Progress report by DTBE on development of the nucleic acid amplification test guidelines.
- Presentation on the large Canadian study of long-term follow-up of TB contacts who were never treated.

TB Country Assistance Program (TB CAP)

Dr. Charles Wells of DTBE reported that TB CAP is a large five-year project sponsored by the U.S. Agency for International Development (USAID) and was established due to several factors. Congressional appropriations for global infectious diseases increased beginning in 2000. Of these funds, $80-$90 million were allocated annually for TB. Sub-agreements were created for USAID, global and regional bureaus and country missions to channel funds to partners. The Global Bureau established the five-year TB Coalition for Technical Assistance (TBCTA) project from 2000-2005 to assist USAID missions that had no previous experience in TB control or programming efforts.

TBCTA served as a partnership between USAID and six TB technical agencies. The project had a limit of $42 million and >50% of funds were provided by USAID missions. CDC received direct funding from TBCTA through an interagency agreement. An evaluation of TBCTA demonstrated positive results and served as the basis for the new 2005-2010 TB CAP initiative. TB CAP funding was awarded in September 2005 and requires grantees to build on the strengths of the TBCTA evaluation and place additional emphasis on TB/HIV, drug management and laboratory capacity building.

TB CAP funding was awarded to three new grantees and all of the original TBCTA partners with the exception of one. CDC and other partners will continue to be funded through an interagency agreement and sub-agreements. TB CAP has a limit of $150 million with $70 million proposed for TB and $80 million proposed for the President's Emergency Plan For AIDS Relief (PEPFAR) for TB/HIV over five years. Estimates show that <20% of TB CAP dollars are used for overhead and administrative expenses, while 80%-85% of funding is allocated to programs at the country level to treat patients and conduct activities.

TB CAP has a stronger strategic design than TBCTA and places more emphasis on the framework for the new 2006-2015 Global Plan for TB Control. The five major components of TB CAP are advocacy and social mobilization, DOTS expansion, laboratory capacity building, TB/HIV, and training and human resource development. Several missions have collectively made an investment of ~$6-$7 million in the short period of time since TB CAP was launched in October 2005. Funds from these missions will be used for country-specific activities. The Global Bureau will provide limited core funds to support the Program Management Unit and conduct cross-cutting activities. The mission in the Philippines intends to use TB CAP in the near future.

Overall, TB CAP has both strengths and weaknesses. On the one hand, TB CAP reflects a strategic application of U.S. government funds and serves as an effective mechanism for coordination among leading TB technical organizations. TB CAP is closely managed by USAID cognizant technical officers to ensure duplication and redundancy in activities and funding streams are minimized. USAID's indicators to measure TB CAP are consistent with existing targets of international programs. TB CAP partners are required to adhere to a high level of accountability. On the other hand, efforts to broadly engage USAID missions to access and utilize TB CAP will be a challenge. Strategies to sensitize and engage PEPFAR to expand TB/HIV activities will also be difficult.

International Standards for TB Care (ISTC)

Dr. Iademarco reported that efforts are underway to develop a set of essential TB care standards for application by all providers and in all patient populations. USAID allocated $200,000 in October 2004 to fund this initiative for two years. An ISTC Steering Committee was formed and is represented by 28 members from 14 different countries to fulfill a two-fold charge. First, evidence-based standards will be developed with seven commissioned systematic reviews. Second, perspectives from various disciplines rather than specific organizations will be provided. The ISTC Steering

Committee held two meetings to determine the scope and content of the guidelines, prepare two drafts and complete the seven systematic reviews.

The draft ISTC document was developed based on several guiding principles. Emphasis was placed on quality TB care of a high standard for all persons. A widely accepted level of care was described and defined in terms of specific actions all public and private practitioners should take with TB patients or suspects. The engagement of all care providers was facilitated in delivering high-quality care for patients of all ages, including those with smear-positive and smear-negative TB, MDR-TB and TB/HIV. Effective patient care to alleviate suffering and prevent, control and cure TB in communities will continue to serve as the ultimate goal and foundation of DOTS and any control effort. The standard of TB care that exists within DOTS needs further promotion all care providers.

Key features of the draft ISTC guidelines are highlighted as follows. The standards apply to all providers in all sectors regardless of circumstances and all patients of all ages with different types of TB disease. All providers must recognize their respective responsibilities to assume a public health function with a high level of commitment to the community and the patient. The standards are consistent with existing international guidelines. Populations that should be evaluated are addressed, including children with extra pulmonary TB and persons with radiographic abnormalities. Specific criteria for smear-negative cases are described. The essential role of microbiological assessments of both smears and cultures is outlined. Details are provided on evaluating HIV-infected persons at risk.

The responsibility of providers in prescribing an adequate regimen and ensuring adherence to treatment is emphasized. Guidance is provided on developing a patient-centered approach for all patients, monitoring patients for responses to therapy, administering HIV tests to all patients and anti-retroviral drugs if indicated, assessing the likelihood of drug resistance, and engaging in consultations for patients at risk for resistance. Requirements are outlined for evaluating high-risk TB contacts and reporting cases. The ISTC Steering Committee is currently addressing several outstanding issues, such as the need to develop country-specific guidelines in addition to the international document, an effective publication strategy, the identification of pilot study sites for dissemination and implementation, and monitoring and evaluation of the guidelines.

The draft ISTC guidelines were presented to the Stop TB Coordinating Board and other key partners to build consensus. Marketing efforts were launched in July 2005 to obtain broad endorsement. The document will be finalized in December 2005 for wide

dissemination, implementation and evaluation. CDC and the other four TBCTA partners have reviewed and endorsed the draft ISTC guidelines. Ongoing efforts will be made for ACET and other organizations to fully support and endorse the document by participating in the dissemination process, placing the logo of a professional society on the guidelines, or assisting in the implementation strategy.

ACET made two suggestions to refine the draft ISTC guidelines. First, the critical need to prioritize TB infection control at the global level should be emphasized. Guidelines are not typically developed with a solid capacity-building plan for country hospitals to actually implement recommendations. Second, the existing language in the document on "high-risk contacts" should be expanded to more fully address community responsibility for exposure.

ACET went on record with its support of efforts that have been made to date to develop the draft ISTC guidelines. The discussion resulted in two **action items.** DTBE will distribute the document to ACET for review and comment. ACET will revisit this issue and inform DTBE of its specific level of "endorsement," such as assisting in the dissemination and implementation strategies or placing its logo on the guidelines.

New ACET Business

Dr. Kawamura opened the floor for ACET to resolve its unfinished business. The first outstanding issue related to the presentation and discussion on the previous day about future opportunities and challenges for TB clinical trials. Drs. Burman and Kawamura drafted a letter to the HHS Secretary with a background section and three specific recommendations to facilitate timely evaluation of new drugs that are likely to revolutionize TB treatment.

ACET placed a motion on the floor to submit the three recommendations to the HHS Secretary as amended. "ACET recommends that: (1) Funding for TB clinical trials be increased by $10 million at a minimum per year (to approximately $25 million) for the next 10 years. (2) Assurances be given for the different arms of DHHS (CDC, FDA, NIH) to fully cooperate in new TB drug development. (3) Funding for TB trials does not directly compete with domestic TB control activities."

The motion to submit the amended recommendations to the HHS Secretary was properly placed on the floor and seconded by Drs. Fluck and Flood, respectively, and **unanimously approved** by ACET. Dr. Kawamura confirmed that ACET liaisons will be provided with an electronic version of the finalized letter. This approach will allow each

organization to duplicate the letter on its respective letterhead for distribution to the HHS Secretary and Congress.

Dr. Kawamura turned the discussion to the second outstanding issue. CDC will soon release the *Guide for Primary Care Health Care Providers: Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection*. ACET should now decide whether its draft statement on TB elimination and the role of primary care should serve as a cover letter to the PCP guide in anticipation of World TB Day and publication of the QFT-Gold guidelines in December 2005. ACET previously agreed that the statement should be structured to define the role of PCPs in TB elimination, describe specific action steps PCPs can take in this effort, bridge traditional gaps between local health departments and PCPs, and enhance communications between these groups. ACET should also determine whether a joint ACET/AMA endorsement should accompany the guide.

Dr. Wanda Walton of DTBE provided additional details on this issue to guide ACET's discussion. DTBE's survey of TB controllers and PCPs throughout the country showed that PCPs will have the greatest impact in TB elimination in LTBI testing and treatment. As a result, the PCP guide was designed to focus on these two areas. DTBE plans to convene a follow-up meeting on TB disparities in the Southeast in May 2006 to update the participants on actions that were taken after the original consultation was held.

ACET's suggestions to refine the cover letter to the PCP guide are outlined below.

- Provide guidance to PCPs on collaborating and communicating with health departments in terms of providing notification when TB patients and suspects move or transfer care from a PCP to a specialty provider.
- Structure the letter as a short, concise and succinct communication with effective messages to a broad audience of PCPs. For example, explain the important role of PCPs in TB elimination. Provide a list of available resources, tools and FAQs.
- Solicit endorsement of the letter from representatives of primary care organizations who attended the meeting on TB disparities in the Southeast.
- Entitle the letter as the "ACET Statement: Think TB."
- Advise PCPs that local public health departments are a valuable resource in providing assistance, referrals and high-quality treatment to TB patients.

ACET resolved the second outstanding issue with several **action items.** Dr. Kawamura will revise the draft statement as a shorter and simpler cover letter and circulate the document to ACET for review and comment. Dr. Litjen Tan, the ACET liaison to AMA,

will facilitate development of a joint ACET/AMA "Dear Colleague" cover letter to the PCP guide. He will also collaborate with CDC to design an AMA toolkit, compile patient materials for PCPs and advertise these resources in *JAMA*. Drs. Gonzales, Kawamura, Nardell and Walton will convene conference calls or communicate by e-mail to develop an FAQ section to accompany the cover letter. ACET expects to complete the revised cover letter and FAQ section by the end of December 2005.

Dr. Kawamura turned the discussion to the third outstanding issue. Dr. Wade Horn is the Assistant Secretary for Children and Families in the HHS Administration for Children and Families. He wrote a letter to Dr. Kawamura in September 2005 letter in response to ACET's March 2005 letter to the HHS Secretary about the outbreak of TB and MDR-TB in Hmong refugees. Dr. Horn responded to ACET's three recommendations as follows. First, reimbursement for refugees is currently not available under the Office of Refugee Resettlement (ORR) within the existing level of appropriated funds. Second, the President's FY'06 budget request for funding to maintain refugee medical assistance benefits for eight months is a level that has not changed since 1991. Third, ORR resources are currently available in the 37 states most affected by Hmong resettlement.

Dr. Kawamura asked whether ACET should take further actions on this issue at the HHS level or shift its focus to developing guidelines at the CDC level. Dr. Valdiserri provided additional details to guide the discussion. He stated that federal advisory committees tend to have the most significant impact by going on record about scientific and technical issues, publishing articles in the *MMWR* or outside journals, and engaging in collaborative efforts with partners that have similar interests.

ACET resolved the third outstanding issue with several **action items.** Drs. Kawamura, Valdiserri and DTBE leadership will convene a conference call to review recommendations made by the ACET Foreign-Born Workgroup and identify areas where concrete action steps can be taken. An e-mail message will be circulated to solicit other volunteers from ACET if additional assistance is needed.

ACET will develop and publish technical recommendations in the *MMWR* on overseas screening, treatment and case management practices for TB and MDR-TB among refugees and immigrants prior to U.S. entry. ACET will collaborate with the U.S. Department of State, DTBE and other relevant federal agencies in this effort. Dr. Kawamura will not respond to Dr. Horn's September 2005 letter, but she will send a short communication to inform him that ACET and CDC will develop technical guidance on TB and MDR-TB among refugees and immigrants in the near future.

Dr. Kawamura turned the discussion to the fourth outstanding issue. ACET agreed to revisit Dr. Menzies's presentation on the previous day about U.S. returns from TB control investments in other countries. ACET resolved the fourth outstanding issue with **action and agenda items**. ACET will summarize key findings from the Menzies, *et al*. study in laymen's terms and distribute the document to the American Lung Association (ALA) for broader dissemination to constituents. The overarching message of the document will be that the United States will reap substantial domestic benefits by investing in TB control overseas.

A presentation will be made at the next meeting on the actual epidemiology of TB in Mexico versus the U.S.-Mexico border. This information will allow ACET to identify areas in Mexico with the largest TB burden that affect the United States. ACET will also be in a position to provide more evidence-based guidance on areas in Mexico in most need of U.S. dollars for TB control.

Another presentation will be made at the next ACET meeting to emphasize the critical need to strengthen TB control efforts in Haiti. Only a small U.S. investment is needed to greatly enhance the primitive TB infrastructure in this country. DTBE will invite representatives of relevant organizations or their designees to the next ACET meeting to provide input on these presentations, including Mr. Hector Martinez of the U.S.-Mexico Border Health Commission, the Assistant Secretary for U.S. Customs and Border Protection, and an expert with extensive experience and knowledge of the Haitian public health infrastructure.

Closing Session

The next ACET meeting is tentatively scheduled for February 15-16, 2006. DTBE will poll the members by e-mail to confirm availability for this date.

With no further discussion or business brought before ACET, Dr. Kawamura adjourned the meeting at 11:55 a.m. on November 17, 2005.